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(FILE 'HOME' ENTERED AT 14:14:10 ON 14 APR 1999)

FILE 'MEDLINE, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH, LIFESCI, HCAPLUS, NTIS, WPIDS' ENTERED AT 14:14:44 ON 14 APR 1999

L1	1392	S	HISTIDINE (A)KINASE?
L2	174805	S	STAPHYLOCOCCUS AUREUS
L3	25	S	L1 AND L2
L4	15		DUP REM L3 (10 DUPLICATES REMOVED)
L5	1178452	S	CLON? OR CHARATER?
L6	8	S	L4 AND L5

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(FILE 'USPAT' ENTERED AT 14:08:12 ON 14 APR 1999)

L1	447	S	435/194/CCLS
L2	5870	S	435/320.1/CCLS
L3	1606	S	435/325/CCLS
L4	2894	S	435/252.3/CCLS
L5	17	S	HISTIDINE KINASE
L6	7	S	L4 AND L5
L7	7935	S	STAPHYLOCOCCUS AUREUS
L8	1	S	L6 AND L7

US PAT NO: 5,854,020 [IMAGE AVAILABLE] L8: 1 of 1
DATE ISSUED: Dec. 29, 1998
TITLE: TCSTS polynucleotides
INVENTOR: John Edward Hodgson, Malvern, PA
Nicola Gail Wallis, Wayne, PA
ASSIGNEE: SmithKline Beecham p.l.c., Brentford, United Kingdom (foreign corp.)
APPL-NO: 08/771,455
DATE FILED: Dec. 20, 1996
ART-UNIT: 165
PRIM-EXMR: Paula K. Hutzell
ASST-EXMR: Khalid Masood
LEGAL-REP: Edward R. Gimmi, Elizabeth J. Hecht, William T. King

US PAT NO: 5,854,020 [IMAGE AVAILABLE] L8: 1 of 1

ABSTRACT:
Novel response regulator polypeptides and DNA (RNA) encoding such polypeptides and a procedure for producing such polypeptides by recombinant techniques is disclosed. Also disclosed are methods for utilizing such polynucleotides and polypeptides for the treatment of infection, particularly bacterial infections. Antagonists against such the polypeptides of the invention and their use as a therapeutic to treat infections, particularly bacterial infections are also disclosed. Also disclosed are diagnostic assays for detecting diseases related to the presence the nucleic acid sequences and the polypeptides of the invention in a host. Also disclosed are diagnostic assays for detecting polynucleotides encoding response regulators and for detecting the polypeptide in a host.
US-CL-CURRENT: 435/69.1; 424/243.1; **435/252.3**, 883; 530/350; 536/23.1, 23.4, 23.5, 24.31

SUMMARY:

BSUM(12)

In another particularly preferred embodiment of the present invention there is a novel protein from **Staphylococcus aureus** comprising the amino acid sequence of FIG. 2 [SEQ ID NO:2], or a fragment, analogue or derivative thereof.

SUMMARY:

BSUM(13)

In . . . aspect of the present invention there is provided an isolated nucleic acid molecule encoding a mature polypeptide expressible by the **Staphylococcus aureus** DNA contained in the National Collection of Industrial and Marine Bacteria Ltd. (NCIMB), Aberdeen, Scotland under number NCIMB 40771 on. . .

SUMMARY:

BSUM(29)

In particular, the invention relates to a novel response regulator protein from **Staphylococcus aureus** WCUH29, characterized in that it comprises the amino acid sequence given in SEQ ID NO: 2 or a fragment, analogue. . .

DETDESC:

DETD(23)

The invention relates to a novel response regulator protein from **Staphylococcus aureus**, characterized in that it comprises the amino acid sequence given in SEQ ID NO: 2 or a fragment, analogue or. . .

DETDESC:

DETD(46)

Using . . . may be obtained using standard cloning and screening procedures, such as those for cloning and sequencing chromosomal DNA fragments from **Staphylococcus aureus** cells as starting material, followed by obtaining a full length clone. For example, to obtain a polynucleotide of the invention. . . as that sequence given in FIG. 1 [SEQ ID NO: 1], typically a library of clones of chromosomal DNA of **Staphylococcus aureus** in E.coli or some other suitable host is probed with a radiolabeled oligonucleotide, preferably a 17-mer or longer, derived from. . .

DETDESC:

DETD(67)

The present invention further relates to a novel **Staphylococcus aureus** response regulator protein which has a deduced amino acid sequence of 243 amino acids in length, as set forth in. . .

DETDESC:

DETD(152)

In . . . a method of screening drugs to identify those which i) interfere with the interaction of the response regulator with a **histidine kinase**, the method comprising incubating the response regulator with **histidine kinase** in the presence of the drug and measuring the ability of the drug to block this interaction; ii) interfere with the ability of the response regulator to catalyse the transfer of phosphate group from the **histidine kinase** to itself, the method comprising incubating the response regulator with drug and measuring the ability of the response regulator to catalyse the removal of phosphate from phosphorylated **histidine kinase**; and/or iii) interfere with the ability of the molecule to autodephosphorylate itself once the phosphate had been transferred, the method. . .

DETDESC:

DETD(153)

The **histidine kinase** is preferably the cognate **histidine kinase** of the response regulator, or another **histidine kinase** which is capable of acting as a substrate for the response regulator, and is preferably from Staph. aureus but may be from another microorganism, e.g., Bacillus. Generally the genes for a **histidine kinase** and its cognate response regulator are found close together on the chromosome so a suitable **histidine kinase** may conveniently be identified by further sequencing along the chromosome.

DETDESC:

DETD(192)

Total cellular DNA is isolated from **Staphylococcus aureus** strain WCUH29 (NCIMB 4077 1) according to standard procedures and size-fractionated by either of two methods.

CLAIMS:

CLMS(2)

2. An isolated polynucleotide encoding the same mature polypeptide expressed by the response regulator gene contained in the

Staphylococcus aureus NCIMB 40771 and comprising the polynucleotide sequence of SEQ ID NO: 1.

CLAIMS:

CLMS(12)

12. The polynucleotide of claim 1, 3, 4, 7 or 8 wherein said polynucleotide encodes a response regulator polypeptide contained in **Staphylococcus aureus**.

L6 ANSWER 1 OF 8 MEDLINE
ACCESSION NUMBER: 1998294999 MEDLINE
DOCUMENT NUMBER: 98294999
TITLE: **Cloning** and characterization of an accessory gene regulator (agr)-like locus from Staphylococcus epidermidis.
AUTHOR: Van Wamel W J; van Rossum G; Verhoef J; Vandenbroucke-Grauls C M; Fluit A C
CORPORATE SOURCE: Eijkman-Winkler Institute for Microbiology, Infectious Diseases and Inflammation, Utrecht University, Netherlands.. w.j.b.vanwamel@lab.azu.nl
SOURCE: FEMS MICROBIOLOGY LETTERS, (1998 Jun 1) 163 (1) 1-9. Journal code: FML. ISSN: 0378-1097.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-Z49220
ENTRY MONTH: 199809
ENTRY WEEK: 19980902
AB The presence of sequences related to the agr of **Staphylococcus aureus** was demonstrated in Staphylococcus epidermidis by agr-specific PCR, and Southern blot. The agr-like locus of S. epidermidis A086 was **cloned** and sequenced. An overall homology of 68% was found between the agr locus from S. epidermidis and S. aureus. The agr locus from S. epidermidis was organized similar to those from S. aureus and S. lugdunensis. The putative RNAII molecule contains four open reading frames, agr A, B, C and D. AgrA was a response regulator. AgrB showed homology with transducer and translocase molecules. AgrC is expected to act as a histidine protein kinase in which a leucine zipper is present. AgrD is presumably processed into an autoinducer peptide. The putative RNAIII molecule contained an open reading frame encoding a putative 26 amino acid (aa) polypeptide, which differed in 3 aa from the RNAIII encoded delta-toxin of S. aureus. Kinetic studies showed that the production of this RNAIII was elevated during the post-exponential phase. delta-Toxin activity was demonstrated for 21 of 23 tested S. epidermidis strains. Kinetic studies of the production of delta-toxin showed that the toxin was produced during the post-exponential phase. Sequencing of S. epidermidis A097, which showed a delayed agr-response, revealed a truncated AgrC lacking the **histidine kinase** domain. These data indicate that an agr-like locus is active in S. epidermidis during the post-exponential phase.

L6 ANSWER 2 OF 8 MEDLINE
ACCESSION NUMBER: 94161498 MEDLINE
DOCUMENT NUMBER: 94161498
TITLE: The gene encoding plantaricin A, a bacteriocin from Lactobacillus plantarum C11, is located on the same transcription unit as an agr-like regulatory system.
AUTHOR: Diep D B; Havarstein L S; Nissen-Meyer J; Nes I F
CORPORATE SOURCE: Laboratory of Microbial Gene Technology, Agricultural University of Norway, As..
SOURCE: APPLIED AND ENVIRONMENTAL MICROBIOLOGY, (1994 Jan) 60 (1) 160-6. Journal code: 6K6. ISSN: 0099-2240.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-X75323
ENTRY MONTH: 199406

AB Purification and amino acid sequencing of plantaricin A, a bacteriocin from Lactobacillus plantarum C11, revealed that maximum bacteriocin activity is associated with the complementary action of two almost-identical peptides, alpha and beta (J. Nissen-Meyer, A. G. Larsen, K. Sletten, M. Daeschel, and I. F. Nes, J. Gen. Microbiol. 139:1973-1978, 1993). A 5-kb chromosomal HindIII restriction fragment containing the structural gene of plantaricin A was **cloned** and sequenced. Only one gene encoding plantaricin A was found. The gene, termed plnA, encodes a 48-amino-acid precursor peptide, of which the 22 and 23 C-terminal amino acids correspond to the purified peptides. Northern (RNA) blot analysis demonstrated that a probe complementary to the coding strand of the plantaricin A gene hybridized to a 3.3-kb mRNA transcript. Further analysis of the 3.3-kb transcript demonstrated that it contains three additional open reading frames (plnB, plnC and plnD) downstream of plnA.
The DNA sequences of plnB, plnC, and plnD revealed that their products closely resemble members of bacterial two-component signal transduction systems. The strongest homology was found to the accessory gene regulatory (agr) system, which controls expression of exoproteins during post-exponential growth in **Staphylococcus aureus**. The finding that plnABCD are transcribed from a common promoter suggests that the biological role played by the bacteriocin is somehow related to the regulatory function of the two-component system located on the same operon.

L6 ANSWER 3 OF 8 MEDLINE
ACCESSION NUMBER: 94028916 MEDLINE
DOCUMENT NUMBER: 94028916
TITLE: **Cloning** and nucleotide sequence of a gene from Lactobacillus sake Lb706 necessary for sakacin A production and immunity.
AUTHOR: Axelsson L; Holck A; Birkeland S E; Aukrust T; Blom H
CORPORATE SOURCE: MATFORSK, Norwegian Food Research Institute, As..
SOURCE: APPLIED AND ENVIRONMENTAL MICROBIOLOGY, (1993 Sep) 59 (9) 2868-75.
Journal code: 6K6. ISSN: 0099-2240.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-Z21855; GENBANK-X62978; GENBANK-X62979; GENBANK-X62980; GENBANK-X62981; GENBANK-X62986; GENBANK-X62987; GENBANK-X62988; GENBANK-X62989; GENBANK-X62990
ENTRY MONTH: 199401

AB Sakacin A is an antilisterial bacteriocin produced by Lactobacillus sake Lb706. In order to identify genes involved in sakacin A production and immunity, the plasmid fraction of L. sake Lb706 was shotgun **cloned** directly into a sakacin A-nonproducing and -sensitive variant, L. sake Lb706-B, by using the broad-host-range vector pVS2. Two **clones** that produced sakacin A and were immune to the bacteriocin were obtained.
A DNA fragment of approximately 1.8 kb, derived from a 60-kb plasmid of

strain Lb706 and present in the inserts of both **clones**, was necessary for restriction of sakacin A production and immunity in strain Lb706-B. The sequence of the 1.8-kb fragment from one of the **clones** was determined. It contained one large open reading frame, designated sakB, potentially encoding a protein of 430 amino acid residues. Hybridization and nucleotide sequence analyses revealed that the **cloned** sakB complemented a mutated copy of sakB present in strain Lb706-B. The sakB gene mapped 1.6 kb from the previously **cloned** structural gene for sakacin A (sakA) on the 60-kb plasmid. The putative SakB protein shared 22% amino acid sequence identity (51% similarity if conservative changes are considered) to AgrB, the deduced amino acid sequence of the **Staphylococcus aureus** gene agrB. The polycistronic agr (accessory gene regulator) locus is involved in the regulation of exoprotein synthesis in S. aureus. Similar to the AgrB protein, SakB had some features in common with a family of transmembrane histidine protein kinases, involved in various adaptive response systems of bacteria.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 4 OF 8 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 98-11158 BIOTECHDS
TITLE: DNA encoding staphylococcal **histidine-kinase**; **Staphylococcus aureus** recombinant protein preparation, DNA probe, and antagonist, used as antibiotic or for infectious disease therapy, gene therapy or nucleic acid vaccine, etc.
AUTHOR: Wallis N G
PATENT ASSIGNEE: SK-Beecham
LOCATION: Philadelphia, PA, USA; Brentford, UK.
PATENT INFO: EP 870831 14 Oct 1998
APPLICATION INFO: EP 98-302776 8 Apr 1998
PRIORITY INFO: US 97-43489 10 Apr 1997
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 98-523158 [45]
AB A new DNA sequence has at least 70% identity to a DNA sequence encoding a specified 363 amino acid protein sequence. Also claimed are: cDNA and DNA with at least 15 contiguous nucleotides of the new sequence (DNA probe); a **Staphylococcus aureus** WCUH 29 (NCIMB 40771) DNA sequence encoding **histidine-kinase**; a vector containing the DNA; a host cell containing the vector; producing the protein using the host cell; an antibody against the protein; and an antagonist which inhibits activity of the protein. The DNA and protein may be used for infectious disease diagnosis, therapy or gene therapy, in a recombinant vaccine or a nucleic acid vaccine, or for drug screening. Diseases associated with expression of the protein include otitis media, empyema, infective endocarditis, secretory diarrhea, cerebral abscess, blepharitis, perinephric abscess, impetigo or osteomyelitis, etc. Antibodies may be used as antibiotics. (30pp)

L6 ANSWER 5 OF 8 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 98-10739 BIOTECHDS
TITLE: New DNA encoding **Staphylococcus aureus** **histidine-kinase** used to prevent, treat, diagnose and vaccinate; against respiratory tract infection, cardiac,

gastrointestinal, central nervous system, eye, kidney, urinary tract, skin, bone and joint disorder
AUTHOR: Wallis N G
PATENT ASSIGNEE: SK-Beecham
LOCATION: Philadelphia, PA, USA; Brentford, UK.
PATENT INFO: EP 863208 9 Sep 1998
APPLICATION INFO: EP 98-301167 17 Feb 1998
PRIORITY INFO: US 97-39478 25 Feb 1997
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 98-458839 [40]
AB An isolated 2,700 bp nucleic acid (A) with at least 70% identity to a nucleic acid encoding an 861 amino acid protein (B), of given sequence, is claimed. Also claimed are nucleic acids complementary to (A), and partial sequences of (A). (A) encodes the mature **histidine-kinase** protein expressed by the gene NCIMB 40771. The claims also cover a vector containing (A), and a host cell transformed by that vector. Also covered are: the protein (B), a protein at least 70% identical to (B), an antibody (Ab) specific to (B), and an antagonist that inhibits (B)'s activity. The claims extend to a nucleic acid that can be obtained by screening a library containing a complete (A) under stringent conditions, and using a DNA probe with at least a partial sequence of (A). This is of use in treating an individual in need of **histidine-kinase**. Either the protein, or the DNA encoding it can be delivered. Alternatively the antagonist of (B) can be used to inhibit **histidine-kinase**. (A) can also be used to diagnose diseases related to (B) expression. (B) can be used to induce an immune response, causing production of (B)-Ab. (31pp)

L6 ANSWER 6 OF 8 BIOTECHDS COPYRIGHT 1999 DERWENT INFORMATION LTD
ACCESSION NUMBER: 98-09561 BIOTECHDS
TITLE: New DNA encoding **Staphylococcus aureus histidine-kinase**; used to screen compounds for antibiotic activity and as vaccines and to treat Staphylococcus infection in e.g. wounds and protheses
AUTHOR: Wallis N G; Shilling L K; Warren R L
PATENT ASSIGNEE: SK-Beecham
LOCATION: Philadelphia, PA, USA; Brentford, Middlesex, UK.
PATENT INFO: EP 857787 12 Aug 1998
APPLICATION INFO: EP 98-300829 4 Feb 1998
PRIORITY INFO: US 97-37856 7 Feb 1997
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 98-416009 [36]
AB An isolated DNA sequence (I) is claimed having at least 70% identity to a sequence encoding a 139 amino acid protein (II) (also claimed). Also claimed are: an isolated DNA sequence with at least 70% identity to a sequence encoding the same protein expressed by the **histidine-kinase** gene in **Staphylococcus aureus** WCUH29; a sequence encoding a protein whose sequence is at least 70% identical to (II); a DNA sequence complementary to (I); a vector comprising (I) and a host cell comprising this; a protein at least 70% identical to (II); antibody against (II); and an antagonist inhibiting the activity/expression of (II). (II) is used to treat an individual requiring **histidine-kinase**. The antagonist can be used to inhibit it. (II) can also be used to diagnose disease related to expression or activity of (II) and as vaccines for and to treat **Staphylococcus aureus** infections. (I) and (II) are used to screen for compounds with antibiotic activity. They are also

used in surgery and to treat wounds, and are also possible prophylactic
antibiotics to prevent late deep infection after insertion of a prosthesis. (23pp)

L6 ANSWER 7 OF 8 SCISEARCH COPYRIGHT 1999 ISI (R)
ACCESSION NUMBER: 95:267936 SCISEARCH
THE GENUINE ARTICLE: QR556
TITLE: THE GENES INVOLVED IN PRODUCTION OF AND IMMUNITY TO SAKACIN-A, A BACTERIOCIN FROM LACTOBACILLUS-SAKE LB706
AUTHOR: AXELSSON L (Reprint); HOLCK A
CORPORATE SOURCE: NORWEGIAN FOOD RES INST, MATFORSK, OSLOVEIEN 1, N-1430 AS,
NORWAY (Reprint)
COUNTRY OF AUTHOR: NORWAY
SOURCE: JOURNAL OF BACTERIOLOGY, (APR 1995) Vol. 177, No. 8, pp.
2125-2137.
ISSN: 0021-9193.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 56
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Sakacin A is a small, heat-stable, antilisterial bacteriocin produced
by Lactobacillus sake Lb706. The nucleotide sequence of a 8,668-bp fragment, shown to contain all information necessary for sakacin A production and immunity, was determined. The sequence revealed the presence of two divergently transcribed operons. The first encompassed the
structural gene sapA (previously designated sakA) and saiA, which encoded
a putative peptide of 90 amino acid residues. The second encompassed sapK
(previously designated sakB), sapR, sapT, and sapE, sapK and sapR presumably encoded a **histidine kinase** and a response regulator with marked similarities to the AgrB/AgrA type of two-component
signal-transducing systems, The putative SapT and SapE proteins shared similarity,vith the Escherichia coli hemolysin A-like signal, sequence-independent transport systems, SapT was the HlyB analog with homology to bacterial ATP-binding cassette exporters implicated in bacteriocin transport. Frameshift mutations and deletion analyses showed
that sapK and sapR were necessary for both production and immunity, whereas sapT and sapE were necessary for production but not for immunity.
The putative SaiA peptide was shown to be involved in the immunity to sakacin A. The region between the operons contained IS1163, a recently described L. sake insertion element, IS1163 did not appear to be involved
in expression of the sap genes, Northern (RNA) blot analysis revealed that
the putative SapK/SapR system probably acts as a transcriptional activator
on both operons. A 35-bp sequence, present upstream of the putative sapA
promoter, and a similar sequence (30 of 35 nucleotides identical) upstream
of sapK were shown to be necessary for proper expression and could thus be
possible targets for transcriptional activation.

L6 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 1999 ACS
ACCESSION NUMBER: 1998:561339 HCAPLUS
DOCUMENT NUMBER: 129:185101
TITLE: **Cloning**, sequence, and expression of **histidine kinase** gene from **Staphylococcus aureus**
INVENTOR(S): Wallis, Nicola Gail; Shilling, Lisa Kethleen; Warren,

PATENT ASSIGNEE(S): [redacted]Richard Lloyd
[redacted]mithkline Beecham Corp., USA; [redacted]thkline Beecham PLC
SOURCE: Eur. Pat. Appl., 23 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 857787	A2	19980812	EP 98-300829	19980204
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CA 2222957	AA	19980807	CA 98-2222957	19980206
JP 11000180	A2	19990106	JP 98-63825	19980206
PRIORITY APPLN. INFO.:			US 97-37856	19970207

AB The invention provides **histidine kinase** polypeptides and polynucleotides encoding **histidine kinase** polypeptides and methods for producing such polypeptides by recombinant techniques. Also provided are methods for utilizing **histidine kinase** polypeptides to screen for antibacterial compds. **Histidine kinase** agonists and antagonist, preferably bacteriostatic, and monoclonal and polyclonal antibodies are also claimed.
The **histidine kinase** and downstream ORF protein sequences were detd. and the genes were **cloned** on expression vectors. **Histidine kinase** shows homol. with the gene degS protein from Bacillus subtilis.

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L1 1392 S HISTIDINE (A)KINASE?
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L5 1178452 S CLON? OR CHARATER?
L6 8 S L4 AND L5

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